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Asymmetric Induction in [1+4] Cycloadditions of Vinyl Isocyanates with Chiral Nucleophilic Carbenes

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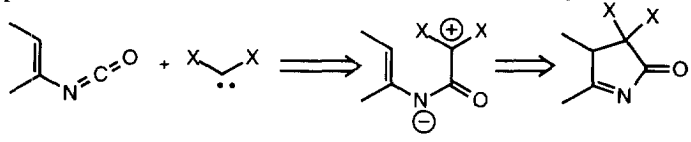
Abstract: Several chirally-modified nucleophilic carbenes afford useful levels of asymmetric induction during [1+4] cycloaddition with vinyl isocyanate reaction partners. Carbenes derived from the 1,2-aminoalcohols (1R,2S)-ephedrine and (1R,2S)-methylaminoindanol proved to be the most effective for delivering high levels of asymmetric induction.

Keywords: Asymmetric induction; carbenes; cycloadditions; indolinones

The utility of nucleophilic carbenes[1] for the rapid assembly of functionally elaborate hydroindolones via a novel [1+4] cycloaddition pathway with vinyl isocyanates has recently been demonstrated.[2] Subsequently, this protocol was employed as the key ring-construction step in a synthesis of (±)-tazettine revealing that this methodology was particularly well-suited to carbon-carbon bond formation in sterically-hindered environments.[3] Based on these observations, this chemistry can offer a potentially general route into various types of hydroindoles that are prominent substructural features of numerous alkaloid ring systems.[4]



The notion that the final ring-closing step of this cycloaddition process may involve a highly-organized transition state suggested that chirally-modified carbene partners could afford products that exhibit significant levels of asymmetric induction. Moreover, to the best of our knowledge, few if any chiral carbenes of this nature have been described previously. In contrast, many chiral metal carbenoids have been reported and studied in detail.[5] A number of enantiomerically pure 1,2-diols are commercially available and could be viewed as potential building blocks for producing the rigid, chiral dialkoxycarbene reactive intermediates needed to examine the viability of this concept, however, most of these species would be expected to readily participate in a facile fragmentation event to yield carbon dioxide and an alkene, a process that forms the basis of the Corey-Winter alkene synthesis.[6] Therefore, these diols were excluded as candidates for these studies. Chiral 1,3-diols, on the other hand, were anticipated to be useful precursors since this fragmentation would no longer be an accessible reaction pathway with these carbenes.

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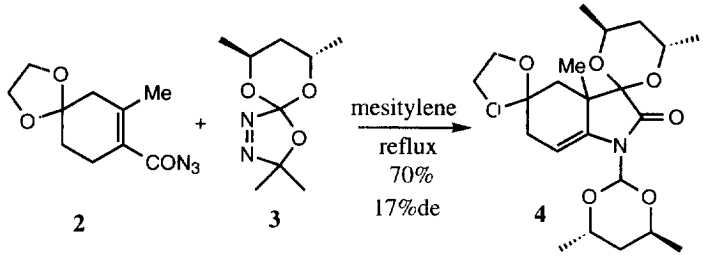
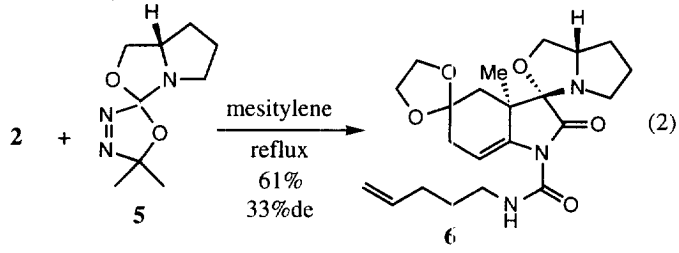
To test this notion several chiral carbene cycloadditions were examined. Thus, exposure of readily available acyl azide **2**,[7] which upon heating gives the corresponding isocyanate, to the oxadiazoline **3**,[8] derived from (2S, 4S)-2,4-pentanediol, in refluxing mesitylene afforded a good chemical yield of the expected 2 : 1 adduct



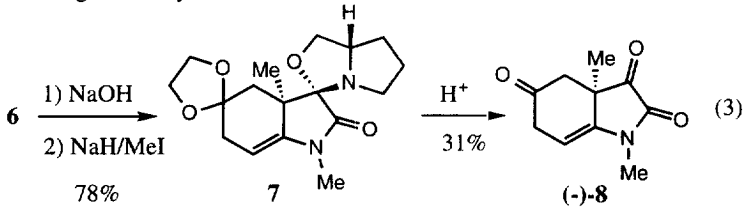
(1)

4.[8] Unfortunately, the level of asymmetric induction noted for this reaction was disappointingly low. Other chiral dialkoxycarbenes were also found to provide good chemical yields of cycloadducts, but, in each case the ring-forming process was accompanied by only low induction levels.



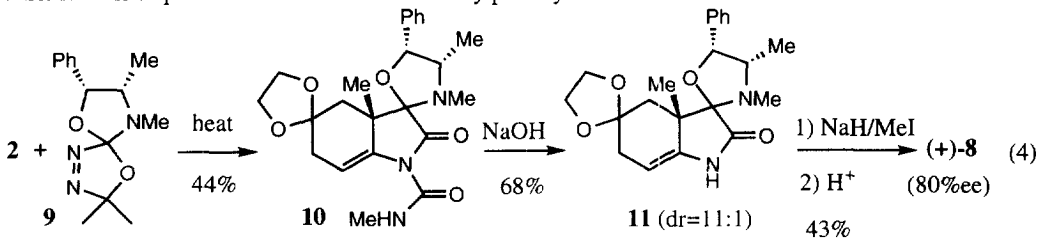
(2)

In light of these results, attention was next directed toward examination of chiral 1,2-amino alcohol-based carbene systems, since we had previously observed that mixed O,N-carbenes of this type also engaged in effective [1+4] cycloaddition with vinyl isocyanates with relatively little interference from the fragmentation side-reaction.[2] Furthermore, it was recognized that a wide variety of enantiomerically pure 1,2-amino alcohol systems were easily available for study. In the event, heating oxadiazoline **5**[8,9] in the presence of isocyanate precursor **2**, under conditions similar to those employed previously, provided a good yield of adduct **6**[8] (major isomer shown) with an encouraging diastereomeric ratio of 2 : 1. The isomers were easily separated, and X-ray crystallographic analysis, after removal of the urea side-chain, revealed the absolute configuration of the major isomer to be as depicted in equation (2). It is noteworthy that the interesting substituent found appended to the enamide nitrogen in **6** appears to be derived from competitive fragmentation of the mixed O,N-carbene intermediate produced during the reaction, an important observation that dictated the use of excess carbene precursor in subsequent reactions performed during this study.

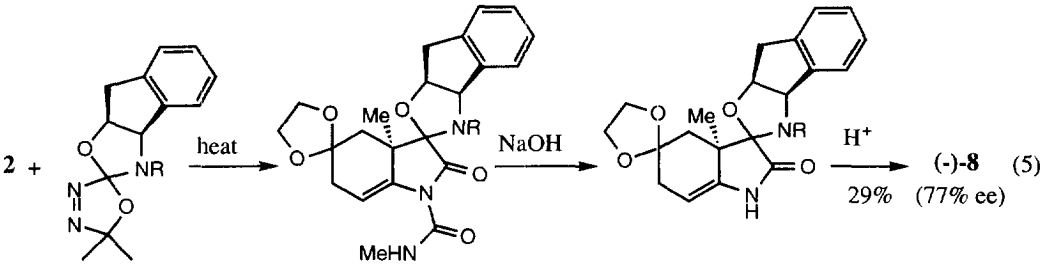


(3)

Ultimately, the synthetic utility of this methodology was critically dependent on the ability to remove the chiral auxiliary after the cycloaddition was complete. After considerable experimentation, a useful conversion of the cycloadduct into the requisite functionalized hydroindolone intermediate was identified that entailed replacement of the urea substituent with a methyl group followed by removal of the amino alcohol under acidic conditions. This sequence afforded enantiomerically pure hydroisatin **8**.[8]



Next, the oxadiazoline **9**,[8] prepared from (1R,2S)-ephedrine, was thermolyzed in the presence of acyl azide **2**, affording adduct **10**[8] in 44% yield as a mixture of at least three isomers as determined by ^{1}H NMR analysis. However, this mixture collapsed to one comprised of only two components **11**[8] (dr = 11 : 1) upon removal of the N-urea substituent, suggesting that a slowly interconverting set of urea rotamers gave rise to the complex mixture seen in the initial cycloadduct **10**. Further processing of **11** as described above afforded **(+)-8**, indicating that the *dextrorotatory* series was formed preferentially in this case.



12a, R=Me
12b, R=n-Pr

13a, R=Me (56%)
13b, R=n-Pr (58%)

14a, R=Me (88%)
dr=10:1

Interestingly, the asymmetric induction observed with carbene precursors (**12a,b**),[8] derived from the Merck (1R,2S)-methylamino indanol auxiliary,[10] proved to be of comparable efficiency to oxadiazoline **9**, however the *levorotatory* compound was produced in excess in this case. Thus, heating **12a** and **2** in the usual fashion afforded **13a**[8] as a complex mixture of isomers, which once again yielded only two diastereomers (dr = 10 : 1) upon base-mediated removal of the urea side-chain. Hydrolysis of the auxiliary under acidic conditions produced **(-)-8** (77% ee). From a synthetic perspective it is significant that the cycloaddition can be brought to practice in stereocomplementary fashion by selecting either the ephedrine- or the aminoindanol-based carbene as the reaction partner. This observation further strengthens the potential utility of this method for general applications to alkaloid synthesis. In a final example, the n-propyl substituted oxadiazoline precursor afforded adduct **13b**[8] in good yield and with reasonable diastereoselection. However, efforts to hydrolyze this material to hydroisatin **8** under a range of conditions proved to be unsuccessful, thus precluding a convenient assay of enantioselectivity in this reaction. Additional studies revealed that carbenes derived from (S)-N-methyl-

phenylalanol and (1S,2R)-2-methylamino-1,2-diphenyl ethanol failed to provide significant quantities of [1+4] cycloadducts.

In summary, rapid access to enantiomerically enriched, highly functionalized hydroindolone products of either enantiomeric series can be conveniently obtained via [1+4] cycloaddition of chiral amino alcohol-derived carbenes with highly substituted vinyl isocyanates. The ability to assemble very hindered quaternary centers with good control of stereoinduction and with reasonable chemical efficiency is a noteworthy feature of this chemistry.

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(7) Prepared from the corresponding α,β-unsaturated carboxylic and by treatment with DPPA.[2]

(8) This compound exhibited spectral (^{1}H NMR, ^{13}C NMR, IR) and analytical (HRMS and/or combustion analysis) data consistent with the assigned structure.

(9) Compound **5** was prepared as follows: Iodobenzene diacetate (11.2 g, 34.8 mmol) in CH_2Cl_2 (200 mL) was added to a solution of [(2S)-2-(hydroxymethyl)pyrrolidinyl] carbonyl acetone hydrazone (6.3 g, 31.6 mmol) in CH_2Cl_2 (200 mL) at 0 °C. The resultant solution was stirred at 0 °C for 2 h and then for 15 h at room temperature. The mixture was washed with $NaHCO_3$ solution, concentrated and purified by column chromatography. Yield: 4.3 g (68%).

(10) (a) Rossen, K.; Pye, P. J.; DiMichele, L. M.; Volante, R. P ; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 6823. (b) Askin, D.; Eng, K. K.; Rossen, K.; Purick, R. M.; Wells, K. M.; Volante, R. P.; Reider, P. J. *Ibid.* **1994**, *35*, 673.